



## UNITED STATES DEPARTMENT OF COMMERCE

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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/070,099	05/26/93	NEWMAN	K 19867.1.0

18M2/0404

18M2/0404

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NTSBB T. T EXAMINER

ART UNIT PAPER NUMBER

1806

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DATE MAILED: 04/04/94

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined  Responsive to communication filed on \_\_\_\_\_  This action is made final.

A shortened statutory period for response to this action is set to expire Three month(s), \_\_\_\_\_ days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

## Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1.  Notice of References Cited by Examiner, PTO-892.  
2.  Notice of Art Cited by Applicant, PTO-1449.  
3.  Information on How to Effect Drawing Changes, PTO-1474.
2.  Notice of Draftsman's Patent Drawing Review, PTO-948.  
4.  Notice of Informal Patent Application, PTO-152.  
5.  \_\_\_\_\_  
6.  \_\_\_\_\_

## Part II SUMMARY OF ACTION

1.  Claims 1-10 are pending in the application.  
Of the above, claims \_\_\_\_\_ are withdrawn from consideration.  
2.  Claims \_\_\_\_\_ have been cancelled.  
3.  Claims \_\_\_\_\_ are allowed.  
4.  Claims 1-10 are rejected.  
5.  Claims \_\_\_\_\_ are objected to.  
6.  Claims \_\_\_\_\_ are subject to restriction or election requirement.  
7.  This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.  
8.  Formal drawings are required in response to this Office action.  
9.  The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are  acceptable;  not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).  
10.  The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_, has (have) been  approved by the examiner;  disapproved by the examiner (see explanation).  
11.  The proposed drawing correction, filed \_\_\_\_\_, has been  approved;  disapproved (see explanation).  
12.  Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has  been received  not been received  been filed in parent application, serial no. \_\_\_\_\_; filed on \_\_\_\_\_  
13.  Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.  
14.  Other

Note claims 9-11 have been renumbered as claims 8-10 to make numbering consecutive in accordance with Rule 1.126.

## EXAMINER'S ACTION

**III. DETAILED ACTION**

15. The numbering of claims is not accordance with 37 C.F.R. § 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 C.F.R. § 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Additionally, claims should be consecutive without skipping numbers. Claim 8 is omitted from the present specification. Accordingly, misnumbered claims 9-11 have been renumbered 8-10, respectively.

16. Applicant's submission of the Information Disclosure Statement field 9/1/93 is acknowledged.

17. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e., failing to provide an enabling disclosure and failing to adequately describe the instant invention.

The specification provides only the competitive inhibition of the binding of cobalalbumin to intrinsic factor. In addition, the instant specification adds the data of figure 2 which purports to show a first order dissociation rate of antibody from intrinsic factor. Applicants urge that the spike and subsequent dissociation in a concentration dependent fashion relates to the competition between the antibody-intrinsic factor in dynamic equilibrium and the B12-intrinsic factor in dynamic equilibrium. Thus, the results of figure two would seem to buttress the conclusion that the 585.3A3A8 antibody merely binds at the binding site to B12-intrinsic factor or in a manner that sterically hinders the binding. Accordingly, applicant's data is suspect.

The description on pages 13 and following of the generation of intrinsic factor antibodies is of a relatively generic nature. Specifically, no particular peptide or epitope is set forth that would teach one of ordinary skill in the art how to reproducibly obtain applicant's preferred embodiments. Note, for example, the use of conventional, commercially available reagents at the bottom of page 14, top of page 15. Accordingly, deposit is required of applicant's 585.3A3A8 antibody to insure availability and viability. See 37 C.F.R. 1.801-1.809.

18. Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

19. Claims 2-8 are rejected under 35 U.S.C. § 103 as being unpatentable over Galfre' in view of Chen.

The claims presently recite a generic kit and method of producing a monoclonal antibody to intrinsic factor as well as generic methods of diagnosis. While a variety of actual steps are recited as are specific cell types, the particulars of the preferred embodiments merely recite a method of obtaining an antibody by traditional hybridoma means.

The Galfre reference provides teachings for the production of antibodies for any particular antigen. Note the reference at the beginning of the second paragraph. The only thing the reference is missing is the particular antigen.

This is provided by Chen. The reference discloses a radioassay using pure intrinsic factor. The presence of a pure antigen renders the antibody to that antigen to be obvious absent clear and convincing showing of unexpected properties in the resultant antibody. The reason for such a determination is that the manufacture of antibodies as of 1991, the priority date of the instant application, was well known. Note the fact that the Chen and Galfre' references were published in 1981. Therefore, the art demonstrated that as much as 10 years prior to the priority of the claimed invention, antibodies specific for intrinsic factor were disclosed.

The instant rejection is being made essentially because the claims seem to be the recitation of different method steps which

are generic to hybridoma antibody production. Therefore, a generic reference to hybridomas was cited with a specific reference to the antigen in question used in combination to render the claims obvious. Should applicants traverse the rejection, the response should include discussion of exactly those elements in the claims which are not technologically obvious over generic hybridoma technology. Absent such limitations, the present rejection cannot be overcome.

It is noted that the claims to the kit are considered obvious over the antibody itself. Should the antibody be patentable, the kit would also and vice versa. The reason for such a determination is that the kit claims elements such as a solid support and the attachment of the antibody to the solid support which is typical in the immunoassay art. For example, the sandwich of an antibody between two antibodies is routine. Moreover, review of the invention disclosed in the specification indicates that the inventive concept is the antibody and the way said antibody binds to intrinsic factor, rather than the combination of the antibody with a kit. Accordingly, the rejection has addressed the antibody exclusively.

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --  
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Smolka.

The claim is broadly drawn in functional terms to an allosteric epitope on intrinsic factor. However, review of the specification to elucidate support for such a claim shows that the specification only provides competitive binding data. Applicants have chosen to interpret this data to mean that the claim antibody composition has allosteric binding affinity. However, the only evidence to support such a conclusion is the competitive inhibition data of figure 1. In the instant filing, applicants have submitted a separate figure 2 which purports to provide dissociation rate data showing first order dissociation. Additionally, the rate of dissociation is directly proportional to the amount of B12 present in solution. The rate of dissociation in a normal first order rate graph shows a linear result plotting  $\ln c/c_0$  against time. The data provided only shows a "relative response" without clearly explaining what this parameter is or to what it is relative. Moreover, the x axis does not show time, it shows "seconds in dissociation phase" which does not provide the requisite time. Therefore, applicant's data does not adequately support the statement in the specification at page 22, line 8, that the dissociation is first order. Accordingly, the current rejection is maintained under the conclusion that the claims merely provide data which shows competitive binding between B12 and IF.

Smolka disclose monoclonals to intrinsic factor. Since the limitations of the claims are met, the claims are anticipated. This rejection can be overcome by the submission of unexpected results for the preferred antibodies.

It is noted that the specification does not actually show the argued embodiments of allosteric binding to intrinsic factor, only competitive binding is disclosed. Note, for example the abstract at line 11 where cobalalbumin binding is inhibited by the claimed antibodies. Notice also the teaching in Smolka where 5 antibodies were capable of inhibiting the binding of Cobalalbumin to IF. Therefore, the embodiments are still considered to be met by the prior art and the information of the Smolka reference is the same as applicants. That evidence is the competitive binding assay set forth in example 6 and figure 1. As concentration of B12 increases, the luminescence decreases. The competitive binding disclosed by Smolka at page 609, top of the left column is the same evidence presented by applicants. Accordingly, the reference is anticipatory.

In addition, applicant's new experiment set forth on page 22 of the instant specification does not overcome the instant rejection under §102 because the supplemental experiment is merely further characterization of the claimed invention. Such an experiment does not serve to distinguish the claimed antibody from the prior art. To completely distinguish their invention from the prior art, applicants are invited to present side-by-side

comparison showing that the binding characteristics of the claimed antibody are different from that of the prior art. Otherwise, no evidence exists of record to show that the prior art antibody would not inherently contain the allosteric characteristics claimed by applicants.

22. Claims 9-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Ellis et al.

The rejected claims are drawn to a generic method of assaying for the presence of B12 in a sample by contacting said sample with intrinsic factor and antibody bound to a support. The Ellis reference teaches a generic method of binding antibody which blocks the binding of intrinsic factor to B12. The limitation of claim 10 to monoclonal antibodies is considered obvious as the generation of monoclonal antibodies from polyclonal antibodies is considered obvious in 1991. Note the discussion in section 19 regarding the dates of Chen and Galfre' concerning the availability of antibodies to intrinsic factor 10 years prior to the priority date. Additionally, the Galfre' reference teaches the manufacture of monoclonal antibodies. Finally, applicant's attention is directed to *Ex parte Ehrlich*, 3 USPQ2<sup>nd</sup> 1011 (BPAI, 1987). Accordingly, the claimed diagnostic assay is considered obvious as is the substitution of bound antibody for bound intrinsic factor. Note especially the teaching in the reference at col. 2, lines 30 and following. The reference teaches the isolation of B12/intrinsic factor complexes from antibody/intrinsic factor complexes.

Moreover, the claims also recite more particularly the intrinsic factor attached to a support. The instant method is merely the substitution of the antibody for the intrinsic factor on the support. Since the two exist in dynamic equilibrium where constant association dissociation occurs, the substitution of bound intrinsic factor for bound antibody is considered to be an obvious variation.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mike Nisbet whose telephone number is (703) 308- 4204.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

  
DAVID L. LACEY  
SUPERVISORY PATENT EXAMINER  
GROUP 180  
*4/1/94*

TMN  
January 9, 1994